

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

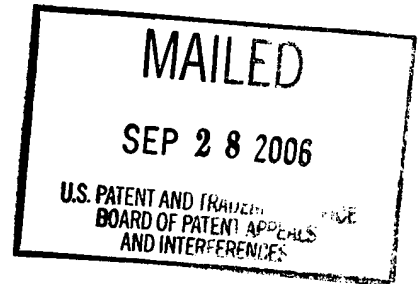
UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte RAYMOND H. BOUTIN

Appeal No. 2006-1879
Application No. 10/010,114

ON BRIEF



Before SCHEINER, GRIMES, and LEOVITZ, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims to a method of transferring nucleic acids into cells, which the examiner has rejected as nonenabled. We have jurisdiction under 35 U.S.C. § 134. Because we conclude that enabling the claimed method does not require providing therapeutically effective gene therapy, we reverse.

Background

Methods for delivering nucleic acids to cells in vivo face several problems: "persistence in the biophase of the organism for a sufficient time to reach the target cell; recognition of the target cell and means for mediating transport of the genetic material through the cell membrane and into the cytoplasm of the cell; avoidance of degradation

within the cell by the reticuloendothelial system; and transport to and through the nuclear membrane into the nucleus of the cell where transcription of the genetic material can take place.” Specification, page 2, lines 5-14. The specification discloses a “multifunctional molecular complex for the transfer of a nucleic acid composition to a target cell comprising . . . : 1) said nucleic acid composition; 2) one or more cationic polyamine components . . . ; [and] 3) one or more endosome membrane disruption promoting components.” Page 12, lines 2-9.

“The core, or backbone[,] of the transfer moiety is the cationic polyamine, containing between 3 and 12 amines.” Page 23, lines 17-18. The function of the cationic polyamine is “to overcome the incompatibility arising from the hydrophilic nature of the nucleic acid molecule and the lipophilic nature of the cell membrane.” Id., lines 20-23.

“The next component of the transfer moiety is the endosome membrane disruption promoting component. . . . This can either comprise one or more lipophilic long chain alkyl groups attached through one or more of the nitrogen atoms of said polyamine, or can comprise a bridging group . . . through which there is attached a fusogenic peptide, or cholic acid or cholesteryl or derivative compound.” Page 25, lines 28-37. This component “prevent[s] degradation of the nucleic acid molecule in a lysosome,” page 16, lines 27-28, by “permit[ting] the complex to escape from the endosome, whereupon it can migrate into the nucleus of the target cell, and release the nucleic acid composition, whose genetic information can then be transcribed within said nucleus.” Page 34, lines 2-6.

Discussion

1. Claims

Claims 1, 2, 5-9, and 17-52 are on appeal. Claims 3 and 4 are also pending; claim 4 has been objected to but not rejected, and claim 3 has been withdrawn from consideration by the examiner.

Claim 1 is representative and reads as follows:

1. A method for the transfer of a nucleic acid composition to cells, comprising the step of introducing a multifunctional molecular complex into cells,

wherein said multifunctional molecular complex comprises:

A) a nucleic acid composition; and
B) a transfer moiety comprising

- (i) one or more cationic polyamine components, wherein each cationic polyamine is non-covalently bound to said nucleic acid composition and comprises from three to twelve nitrogen atoms; and
- (ii) one or more endosome membrane disruption promoting components attached to at least one nitrogen atom of at least one of said polyamine components through an alkyl, carboxamide, carbamate, thiocarbamate, or carbamoyl bridging group, said one or more endosome membrane disruption promoting components independently selected from (a) at least one lipophilic long chain alkyl group or (b) a fusogenic peptide, cholic acid or cholesteryl group or a derivative thereof;

wherein said multifunctional molecular complex transfers said nucleic acid composition to said cells.

Thus, claim 1 is directed to a “method for the transfer of a nucleic acid composition to cells.” The claim is not limited to cells in culture or in a subject, so the claim encompasses both in vitro and in vivo methods. The claimed method comprises “introducing . . . into cells” a multifunctional complex comprising a nucleic acid composition; a cationic polyamine comprising three to twelve nitrogen atoms,

noncovalently bound to the nucleic acid composition; and an endosome disrupting agent (which can be a lipophilic long chain alkyl group, a fusogenic peptide, cholic acid, a cholesteryl group, or a derivative) attached to a nitrogen of the polyamine component via specified linkages.

2. Enablement

The examiner rejected claims 1, 2, 5-9, and 17-52 under 35 U.S.C. § 112, first paragraph, for nonenablement. The examiner focused on the aspect of the claimed method that involves transferring a nucleic acid encoding a therapeutic protein into cells.¹ The examiner concluded that the specification is enabling for a method of transferring a nucleic acid encoding a therapeutic protein into cells in vitro but is not enabling for the same method carried out in vivo. See the Examiner's Answer, page 3.

The examiner reasoned that "[t]he in vivo aspect of claims 1, 2, 5-9 and 17-52 is interpreted as gene therapy as the specification does not disclose a use for delivering a therapeutic protein other than for therapeutic purposes." Id. The examiner noted that the instant application has an effective filing date of September 28, 1994,² and cited several references as evidence that undue experimentation would have been required to successfully carry out gene therapy as of that date. Id., pages 4-6.

The examiner noted that the specification does not "disclose any particular DNA sequences that can be administered by applicant's claimed methods" to treat any

¹ The examiner restricted the claims based on the type of protein encoded by the transferred nucleic acid. See the restriction requirement mailed August 13, 2003. Appellant elected the claims directed to a method of transferring a nucleic acid encoding a therapeutic agent. See the paper filed September 11, 2003. The examiner has stated that "[b]ased on this election . . . claims 1, 2[,] 4-9, [and] 17-52, are interpreted as methods of delivering a therapeutic agent using applicant's novel multifunctional molecular complex." Examiner's Answer, pages 7-8.

² The instant application claims benefit under 35 U.S.C. § 120 of the filing date of application serial number 08/314,060, filed September 28, 1994.

specific disease. Id., page 6. The examiner summarized the most relevant working examples:

Example 11 teaches the expression of lacZ when a plasmid comprising a β -galactosidase gene complexed to a transfer moiety of the invention is injected into mouse thigh muscle. . . . Example 12 teaches the finding of hepatitis B [virus] surface antigen in the blood [of] mice injected i.v. with a multifunctional molecular complex comprising a plasmid containing a hepatitis B virus surface antigen gene complexed to a transfer moiety of the invention.

Id., pages 6-7. The examiner found that these examples did not provide sufficient guidance, however, because “in neither case does the expression of the delivered gene result in an alleviation of a symptom of any disease.” Id., page 7.

Appellant argues that “[s]ince the claims do not require a therapeutic effect, Applicant need not demonstrate such an effect in order to enable the claimed subject matter.” Appeal Brief, page 4. Appellant argues that he “need[] only establish that the application enable[s] one of ordinary skill in the art to make and use a method for transfer[ring] nucleic acid compositions to cells . . . without undue experimentation.” Id. Appellant argues that the references cited by the examiner are not applicable because they describe different methods of delivering nucleic acids to cells. Id., page 5. Finally, Appellant relies on a declaration submitted under 37 CFR § 1.132, which is said to provide additional examples of in vivo transfer of nucleic acids using the claimed method. See id., pages 7-9

The examiner bears the initial burden of showing that a claimed method is not enabled. See In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (“[T]he PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately

enabled by the description of the invention provided in the specification of the application.”).

The invention that must be enabled to satisfy § 112 is the invention defined by the claims. See CFMT, Inc. v. Yieldup Int’l Corp., 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003) (“Title 35 does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect.”). Thus, when the claims are not directed to a method that achieves a therapeutically useful result, achieving such a result is not required for the claims to be enabled.

Here, the claims, as restricted, are directed to a “method for the transfer of a nucleic acid composition [encoding a therapeutic agent] to cells.” Thus, while the claims read on gene therapy methods, they do not require producing a clinically effective therapeutic response. Cf. In re Cortright, 165 F.3d 1353, 49 USPQ2d 1464 (Fed. Cir. 1999) (claims to a method of “treating scalp baldness” could be enabled even if the method did not produce a full head of hair).

The examiner argues, however, that the specification must nonetheless teach how to use the claimed method to produce a therapeutically useful result:

[T]he only use disclosed for in vivo delivery is [] for therapeutic purposes. . . . Thus, while the specification enables delivery and expression in cells in culture or cells in vitro, the method of delivering has no enabled use for delivery to cells in an animal, patient or subject[;] that is[,] in vivo. There is no evidence that the method results in sufficient delivery of a nucleic acid in vivo to offer a therapeutic effect. The specification offers no use for mere delivery of a therapeutic agent in vivo absent a therapeutic effect.

Examiner’s Answer, page 8. As we understand it, the examiner does not dispute that the specification enables those skilled in the art to transfer nucleic acids into cells in

vivo, but she argues that transferring a nucleic acid encoding a therapeutic protein does not produce a useful result unless it confers a therapeutic benefit.

The examiner's reasoning highlights the incorporation into § 112 of the utility requirement of 35 U.S.C. § 101: to be enabled, a claimed method must be disclosed sufficiently to allow those skilled in the art to carry out the recited steps and, in addition, the result of the claimed method must have a specific and substantial utility. See In re Fisher, 421 F.3d 1365, 1378, 76 USPQ2d 1225, 1235 (Fed. Cir. 2005) ("It is well established that the enablement requirement of § 112 incorporates the utility requirement of § 101."); In re Kirk, 376 F.2d 936, 942, 153 USPQ 48, 53 (CCPA 1967) ("[S]urely Congress intended § 112 to pre-suppose full satisfaction of the requirements of § 101. Necessarily, compliance with § 112 requires a description of how to use presently useful inventions, otherwise an applicant would anomalously be required to teach how to use a useless invention.").

The examiner's reasoning is logical but we do not agree that it supports rejecting the instant claims. The specification describes experiments in which exogenous DNA was transferred, using the claimed method, to muscle cells and liver cells in vivo. See pages 77-78. The examiner does not dispute the accuracy of these working examples, but points out that the transferred DNAs did not encode therapeutic proteins and the specification does not describe therapeutically effective gene therapy.

The examiner has cited several references to show that clinical application of gene therapy faced many hurdles in 1994. The examiner has characterized the references as showing that delivering therapeutic genes to cells in vivo and ensuring adequate expression of the gene products were major areas of unpredictability at the

time of filing. See the Examiner's Answer, pages 4-6. Appellants argue that the examiner's references are not relevant to the claimed method. See the Appeal Brief, pages 5-6.

We need not resolve this dispute: even if we were to accept, for discussion purposes, both that gene therapy is the only in vivo use disclosed in the specification for the claimed method and that the references show that therapeutically effective gene therapy would have required undue experimentation in 1994, we would still conclude that the record does not support rejecting the claims as nonenabled.

As discussed above, the claims are not directed to a method of carrying out gene therapy, but to a method of transferring nucleic acids into cells. That is, the claimed method is directed to one step in, for example, a gene therapy method. The claimed method is disclosed to overcome some of the problems discussed in the references cited by the examiner. See the specification, page 2:

The problems faced by [nonviral vectors or carriers] include . . . means for mediating transport of the genetic material through the cell membrane and into the cytoplasm of the cell; avoidance of degradation within the cell by the reticuloendothelial system; and transport to and through the nuclear membrane into the nucleus of the cell where transcription of the genetic material can take place.

(emphases added) and page 16:

This multifunctional molecular complex comprises essentially the combination of two key elements, (I) the nucleic acid composition which it is desired to transfer to the target cell, and (II) the transfer moiety, which . . . comprises several components whose function is . . . ii) to overcome the incompatibility . . . [between] the nucleic acid molecule and . . . the cell membrane so that the former can pass through the latter; and iii) to prevent degradation of the nucleic acid molecule in a lysosome of said target cell, by disrupting the pre-lysosome, endosome formation stage.

(Emphases added.)

The examiner has stated that the in vitro embodiments encompassed by the claims are enabled, and has not disputed the accuracy of the specification's in vivo working examples. There seems to be no dispute, therefore, that the claimed method results in the transfer and expression of nucleic acids in targeted cells. We cannot agree that such a result must provide a therapeutic effect in order to be useful.

A method that overcomes some of the problems plaguing the field of gene therapy would seem to be useful, per § 101, even if the method does not resolve all of the problems facing the field. A method that enhances the efficiency of transfer of nucleic acids to cells in vivo, as the present method is said to do, provides a valid research tool that those skilled in the art could use in carrying out experiments that involve transferring nucleic acids to cells in vivo. Thus, such a method is useful to those skilled in the art even if it is not sufficient, by itself, to allow immediate practice of gene therapy.

The present claims are different from, for example, the invention at issue in In re Fisher, 421 F.3d 1365, 76 USPQ2d 1225 (Fed. Cir. 2005). The applicant in that case claimed expressed sequence tags (ESTs) from genes of unknown function. See id. at 1373, 76 USPQ2d at 1231. The court concluded that “the claimed ESTs act as no more than research intermediates that may help scientists to isolate the particular underlying protein-encoding genes and conduct further experimentation on those genes. . . . Accordingly, the claimed ESTs are . . . mere ‘object[s] of use-testing,’ to wit, objects upon which scientific research could be performed with no assurance that anything useful will be discovered in the end.” Id.


The Fisher court considered the applicant's argument that an EST is a research tool, like a microscope, but found the analogy inapt: "[A] microscope has the specific benefit of optically magnifying an object to immediately reveal its structure. One of the claimed ESTs, by contrast, can only be used to detect the presence of genetic material having the same structure as the EST itself. It is unable to provide any information about the overall structure let alone the function of the underlying gene." Id. The court concluded that "Fisher's asserted uses are insufficient to meet the standard for a 'substantial' utility under § 101." Id.

The ESTs at issue in Fisher lacked substantial utility because they were useful only for conducting experiments on the genes of which the ESTs were part; they were not useful for conducting research generally but only for conducting research to learn more about the ESTs themselves and the genes from which they were derived. Here, by contrast, the claimed method is broadly useful for transferring nucleic acids into cells. The instant claims are directed to a completed invention, rather than a "research intermediate" as in Fisher, and can be used to carry out research using a variety of nucleic acids, cells, and subjects. Thus, the instantly claimed method is a valid research tool that can be used to carry out research in general rather than research limited to discovering information about the claimed invention itself.

Summary

We do not agree with the examiner that enabling the instant claims requires enabling therapeutically effective gene therapy. The specification provides adequate guidance to enable those skilled in the art to use the claimed method to transfer nucleic acids to cells, and that is all that the claims require. The rejection for lack of enablement is reversed.

REVERSED



Toni R. Scheiner
Administrative Patent Judge



Eric Grimes
Administrative Patent Judge



Richard M. Lebovitz
Administrative Patent Judge

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